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ABSTRACT

The review and analysis of the current status of knowledge about schizophrenia and its treatment begins with a brief review of some statistics on mental health, the National Institute of Mental Health's grants program in schizophrenia, an NIMH-sponsored international conference on Schizophrenia - the Implications of Research Findings for Treatment and Training, and the Center for Studies of Schizophrenia. A synthesis of recent and current research in schizophrenia covers the following topics: diagnosis, description, and psychological functions; genetics; biology; studies of populations at high risk; family interaction and processes; childhood schizophrenia and autism; and treatment. Problems of two types facing schizophrenia are noted - attitudinal barriers and issues of scientific fact. Six of the most pressing unresolved or controversial scientific questions are detailed. References for each topic discussed are listed. (KW)

# SPECIAL REPORT: SCHIZOPHRENIA

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NATIONAL INSTITUTE OF MENTAL HEALTH

Center for Studies of Schizophrenia

# SPECIAL REPORT: SCHIZOPHRENIA

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*SCHIZOPHRENIA*

*THE PROBLEM*

*For the past 15 years we have been able to report steady decreases in the numbers of resident patients in State and county mental hospitals. Nationwide, this trend is not only continuing but seems to be accelerating; it has meant a more than 30 percent decrease in the number of patients hospitalized with schizophrenia. During 1968, for example, resident patients in State and county mental hospitals declined from 210,000 to 195,000. Despite these very hopeful statistics and the seeming acceleration in the rate of decline in chronicity, significant problems remain: Over the last 15 years admission rates have continued to rise. In 1968 alone, there were more than 320,000 episodes of illness diagnosed as schizophrenia in the United States. The cost of schizophrenia to our country is correspondingly great--estimated at 14 billion dollars annually. This figure represents the indirect as well as the direct costs being borne by society for the two to three million living Americans carrying this diagnosis. The rising admission rate seems to be, in part, a result of multiple hospital stays of individual patients. Thus, there has developed, over the last decade and a half, a "revolving door" phenomenon; patients are being hospitalized for shorter periods than previously, but they are also being more frequently readmitted. The probability of readmission within two years of discharge from an initial episode of schizophrenia, for example, varies between 40 and 60 percent, depending on the study. In the U.S., between 15 and 25 percent of discharged schizophrenics will eventually be readmitted and receive continued care for a prolonged period of time. Furthermore, and perhaps more distressing, is the fact that only 15 to 40 percent of schizophrenics living in the community achieve what might be termed an average level of adjustment (i.e., being self-supporting or successfully functioning as a housewife). These figures indicate a need for more research to determine ways in which discharged patients can be maintained in the community, as well as further study of the effect of family, drugs, work and recreation on community adjustment. Such studies might make possible the development of therapeutic interventions to prevent schizophrenia's recurrence and, at the same time, maximize the former patient's level of psychosocial functioning.*

*The NIMH's Office of Biometry has recently reported some rather remarkable and puzzling statistics on mental health care in our two largest states. In 1968 California had nearly 11,000 patients residing in State and county mental hospitals with functional psychoses (more than 80 percent of these were schizophrenic) whereas New York, with an almost equal population base, had 49,000 resident patients. These figures, taken in conjunction with admission data, reveal a rate of treated functional psychosis in New York nearly five times as great as that for California. This disparity cannot be accounted for (assuming no differential systematic reporting error) by correspondingly higher admission rates for other California facilities, such as general hospitals, V.A.*

*hospitals, private hospitals or outpatient clinics. In these facilities, too, the resident population figures for California were generally lower than the corresponding figures for New York (although the differences were not nearly so great for these facilities as for State and county mental hospitals). In terms of facilities available (other than State and county mental hospitals) California exceeds New York only in number of transitional facilities--for example, halfway houses and nursing homes. It seems unlikely, however, that this magnitude of difference in both resident and newly admitted patients can be attributed to the differential availability of transitional facilities. Although the period 1963-1968 was marked by a decline in resident patients in both California and New York, the former's resident population decreased by 50 percent, as compared to a decline of approximately 20 percent in the latter. It is interesting to note that in 1968 the State of New York had over 90,000 beds available for psychiatric patients, whereas California had fewer than 30,000--a difference largely attributable to New York's having 25 State hospitals and California's having only 12 such facilities (it may be asked whether Parkinson's law is operating in each case). Additional reasons for differences in schizophrenia's prevalence in our two most populous states are complicated and difficult to disentangle, but several possible contributory factors suggest themselves: In the early 1950's California's mental health planners concluded that continuously increasing provision of State hospital beds could lead only to ever-spiraling financial and staffing difficulties in the future. Basing their projections on then-current statistics on population growth and average length of hospital stay, they decided that to cope adequately with the predicted increases in numbers of patients would be impossible. It was therefore decided to abandon the effort to build more and more hospitals and provide more and more beds; rather, they determined to adopt a strategy called the "total push" program for resident patients and a very active treatment of newly admitted cases. This program, underway before the introduction of major tranquilizing agents, was also accompanied by more social service to plan community placement and the development of needed community resources. These administrative planning decisions also resulted in a redefinition of discharge readiness; no longer was "cure" the goal. Discharge was now planned as soon as preillness level of functioning was restored. These changes are often considered responsible for the leveling off of California's chronic population which was already apparent by the time the psychotropic drugs were introduced. In 1958, only shortly after the tranquilizer's introduction, California already had only one-third as many resident psychotic patients as New York, whereas, nationwide, an actual decline in resident schizophrenic patients did not become evident until 1963 (although a plateau had been reached in 1958). Thus, it appears that California had a head start on New York (and most of the nation) in terms of its community-oriented treatment programs. More recently, as part of a new legislative and fiscal policy of decentralization of mental health care, California has*

increasingly used State money to support local facilities and further deemphasized State hospital programs. The factors mentioned above, and doubtless many others, have altered the nature of care delivered and, at the same time, have been associated with vastly lower numbers of resident patients in California than in its Eastern counterpart, New York. Continuing in the vanguard, California has been the first state in the nation to close a State hospital, and plans are underway to close yet another. The differences seen in California raise perplexing questions: What are the effects on individuals, families, and the community as a whole of maintaining more schizophrenic patients outside the hospital? Is it possible that the planning of treatment delivery can so greatly effect the occurrence of a disorder like schizophrenia? Finally, if State planning can have effects of such magnitude, what implications does this have for our thinking about the causes of schizophrenia?

## THE NIMH EFFORT

Since 1948 the National Institute of Mental Health's grants program in schizophrenia has grown from the support of nine research projects at a cost of $113,000 to the allotment in 1970 of more than $18,000,000 for the support of over 350 projects, including, for example, the Hospital Improvement Program, the Hospital Staff Development Program, and a host of training fellowships. Excluded from this sum is the Institute's spending on training and community mental health centers, because the exact percentage of this expenditure directed toward schizophrenia is difficult to estimate--although a substantial number of these programs do, in fact, deal with this disorder. In fiscal year 1970, 77 new research grants related to schizophrenia were funded at a cost of nearly $4,000,000.

### Conference on Schizophrenia

As part of NIMH's continuing effort to speed the practical application of research findings and to evaluate the effectiveness of its programs toward this end, the Institute in collaboration with the National Institues of Health's John E. Fogarty International Center, cosponsored an important international conference, "Schizophrenia--the Implications of Research Findings for Treatment and Training." As conceived by its NIMH organizers--the Planning Branch, the Clinical Research Branch and the Center for Studies of Schizophrenia--the conference's primary purpose was to arrive at recommendations for mental health planning over the next decade. In making their suggestions, the 75 invitees, who represented seven nations--Norway, Finland, England, Denmark, Belgium, Japan and the United States--were asked to consider the "hard" research findings currently available, the nature of present-day training related to schizophrenia, and the kinds of treatment programs and facilities now in existence. Facilitating this endeavor was the constant exchange of information throughout the conference between conferees whose interest lay primarily

in research and participants who were actively involved in the training of clinicians and in the treatment of schizophrenic patients. This process of mutual education and stimulation was enhanced by an emphasis on small discussion groups, which made possible lively and relatively informal discussions.

Because a substantive record of the full conference will be published later, its details will not be spelled out here. It may be useful, however, to highlight some of the topics covered during the course of the meetings. Among the research developments discussed were the following: Advances in the field of classification which have led to more reliable diagnostic methods, progress in the understanding of the nature of schizophrenic thought disorder, further delineation of the role of genetics in schizophrenia's etiology, and recent developments in the "high risk" area of research.

Although generally agreed as to the phenothiazines' efficacy in schizophrenia, many conferees stressed the need for further research to identify 1) patient subgroups particularly responsive to certain drugs and 2) patient subgroups in whom drug administration may interrupt a natural restitutive process and thereby lead to developmental arrest and unnecessary impairment. Also, while our knowledge of the effectiveness of drugs was deemed quite extensive, the unavailability of comparable data on the relative value of the various psychosocial treatments (whether used alone or in conjunction with drug treatment) did not go unnoticed.

Some participants voiced the concern that compartmentalization between units within treatment facilities and rapid staff turnover made continuity of care extremely difficult to deliver to any given patient, possibly resulting in unnecessarily long hospital stays; it was recommended that, in future planning, special emphasis be placed on this problem, as it tends to perpetuate preexisting confusion in the lives of the patients. The lack of community-based nonhospital facilities was also noted, and the conferees recommended that a number of types of supportive community facilities be developed as alternatives to the 24-hour supervision of the psychiatric ward and the rather nonintensive outpatient care currently available.

Addressing themselves to problems of mental health manpower and its distribution, the participants suggested that mental health centers be staffed along functional rather than academic-professional lines--that is, that role allocation within facilities be made on the basis of competence rather than specific profession or academic degree. Because of the shortage of highly trained manpower, many participants stressed the need for a new kind of paraprofessional, one who would play an important role in the primary treatment of patients. The development of this new occupational role was considered indispensable because patients often

distrusted professionals identified with a power structure that is perceived as indifferent. But unless functions and rewards appropriate to his new status are made available, the paraprofessional will continue to feel himself a second-class citizen in a hierarchy dominated by mental health "professionals," and this interesting, potentially valuable experiment will ultimately end in failure.

The problem of integrating recent research findings into clinical practice suggested a new approach to the accreditation of mental health facilities. It was recommended that a team of experienced professionals, knowledgeable about research results and successful treatment programs, travel from institution to institution with the primary purpose of communicating information rather than verifying that each facility is meeting minimal standards of care. The conferees also recognized that those institutional relationships (especially compartmentalization) which prevent the use of research information in the traning process should be carefully scrutinized. All too often, it was felt, researchers are isolated from ongoing training programs and, in fact, contribute to this isolation by failing to consider the changing context of psychiatric treatment in planning their projects; as a consequence, research results are sometimes seen by practitioners as relevant to past rather than to present or future practice.

A notable feature of the entire conference was the optimism which pervaded its sessions. No longer does schizophrenia seem an insoluble riddle with a hopeless outcome. Based on their evaluation of the current "state of the art," these participants found much to be hopeful about despite the universal recognition that significant problems remain.

Center for Studies of Schizophrenia

Brought into a single office nearly two years ago, the Center's functions are three-pronged: information dissemination, program evaluation and development, and program coordination. To increase the flow of communication about the most prevalent major mental illness, the Center publishes, in conjunction with the National Clearinghouse for Mental Health Information, the Schizophrenia Bulletin. Two issues of this new publication have now appeared, and their reception within the field has been gratifying. Also important to the Center's program of information dissemination is the wide distribution of this Special Report and the provision of lecturers to many institutions.

During fiscal year 1970, four major program areas were identified by the Center as warranting special attention: 1) A review of the recent biology of schizophrenia; such a review will appear in the fourth issue of the Schizophrenia Bulletin. 2) The development of research on individuals at relatively high risk for the development of schizophrenia. Toward this

*end, the Center cosponsored, with the Adult Psychiatry Branch of the Intramural Research Program, a small workshop to look at methodologic problems hampering such studies; a report of this conference appeared in the Fall 1970 issue of the Bulletin. In addition, four entirely new studies of this problem were reviewed, approved and funded over the past two years and several others are in the planning stage. 3) Studies of the psychosocial treatment of schizophrenia. As noted in the conference discussed above, too little is known about the effect of various psychosocial interventions in schizophrenia. In hope that it will serve as a paradigm for other studies of psychosocial treatment, the Center has initiated a collaborative study in which schizophrenia is treated as a developmental crisis through which the patient can be guided toward subsequent reintegration at a potentially higher level. Additional studies of various psychosocial treatments in schizophrenia are being planned at present and developments will be reported subsequently. 4) Studies of the diagnostic process. Technical difficulties with film development have delayed this aspect of the Center's program, but we hope to be able to make a diagnostic film interview (which will feature definitions and examples of commonly used descriptive terms) widely available for research and training in the near future.*

*In summary, the Institute's efforts over the last decade seem to have resulted in substantial changes in attitude, scientific sophistication, and types of treatment available for schizophrenia. As with all advances, many new and as yet unanswered questions have been raised, and much of what we call "progress" is still in need of further evaluation, refinement, and redefinition.*

*DIAGNOSIS, DESCRIPTION AND PSYCHOLOGICAL FUNCTIONS*

*First differentiated from other psychoses by Kraepelin in 1896, schizophrenia has been the focus of controversy ever since. To this day, profound disagreement exists as to what properly constitutes schizophrenia and how--or whether--this complex disorder should be subclassified. Recent research on diagnosis has sought to develop more reliable diagnostic instruments and to delineate more homogeneous subgroups within the heterogeneous schizophrenic "syndrome," the latter being especially important for research which attempts to focus on causes.*

*A major obstacle in any attempt to reach agreement as to what schizophrenia is, is the fact that confusingly diverse diagnostic procedures are used in different countries and, indeed, even within a single nation. Recognizing this far-reaching communication problem, participants in the World Health Organization's International Pilot Study of Schizophrenia (IPSS) (1) are developing diagnostic techniques designed to standardize psychiatric classification across cultures. As a first step in this effort, pilot interview schedules have been devised which, it is hoped, will eventually*

*serve as the basis (in further refined form) for future comparative studies of epidemiology, cultural and biological factors, etc. Collaborating in this ambitious study are centers in Columbia, Czechoslovakia, Denmark, Nigeria, India, Taiwan, England, the United States and the Soviet Union. During the past year, analysis has begun of data collected in interviews with 135 patients seen in each of the participating countries. Forms for evaluating course of illness and changes in social function have been developed, tested, and revised; and initial followup interviewing of these patients is now underway.*

*A serendipitous finding during data evaluation at the U.S. Center was that patients described a variety of experiences which might be termed "semidelusional" and "semihallucinatory." This suggests that the practice of viewing delusions and hallucinations as discrete, discontinuous phenomena that are either present or absent in a given patient may be invalid. In order to conceptualize schizophrenia more accurately, it may be necessary to conceptualize such experiences as continous--i.e., as ranging from borderline delusion- or hallucination-like experiences to fullblown delusional or hallucinatory states.*

*In a smaller cross-national study, an interdisciplinary research team located in New York and London (2) has attempted to determine whether the frequently cited differences in the incidence of schizophrenia and depressive illness in England and the United States reflect differing diagnostic practices on the part of British and American clinicians or real cultural differences in the incidence of these disorders in the two countries. The major finding has been that, when standard interview techniques are used, statistical differences between the occurrence of schizophrenia and depression in the two countries all but disappear. This would indicate that the differing rates for these illnesses are more related to differences in diagnostic practices than to the patients themselves. Further analysis based on ratings of psychopathology and diagnosis made by American and British psychiatrists who had observed identical videotapes of doctor-patient interviews led these investigators to conclude that a substantial segment of the diagnostic disparities could be accounted for by the different ways of evaluating mood in the United States and Great Britain. Patients tended to be diagnosed schizophrenic by American psychiatrists if they showed some disorganization of thought (even if this was associated with a marked mood disturbance), whereas British psychiatrists were inclined to diagnose the same patients as suffering from an affective disorder. These results may mean that some U.S. patients receive incorrect treatment (e.g., tranquilizers instead of antidepressants) for their illness.*

*Over a period of years, an East Coast investigator (3) has evolved standardized techniques for evaluating psychopathology which are capable of reliably distinguishing between schizophrenics and other diagnostic groups and also of discriminating among schizophrenic subgroups. With*

*the advent of modern computer technology, this investigator has been able to develop computer programs based on his techniques. Taking the results of a psychiatric examination as input, the program acts as the clinician in subjecting the data to a series of questions and then yielding a psychiatric diagnosis based on its conclusions. As these computer-derived psychiatric diagnoses have demonstrated high agreement with clinical diagnoses made from the same data, they may constitute a rapid, reliable means of selecting schizophrenic subjects for research studies--previously a tedious, error-laden procedure.*

*For some time, schizophrenics have been subclassified into "process" schizophrenics (characterized by gradual, insidious onset of symptoms and poor premorbid social adjustment) and "reactive schizophrenics" (characterized by acute onset of symptoms and good premorbid social adjustment). To test the hypothesis that the process schizophrenic prefers distant interpersonal relationships, an NIMH-supported investigator (4) administered a measure of "psychological distance" to a group of male psychiatric patients. Surprisingly, he found little association between the expressed preference for interpersonal distance and poor premorbid status. These findings, therefore, suggest that the process schizophrenic's history of poor social adjustment may reflect a long standing self-protective maneuver rather than a conscious desire for interpersonal separation.*

*The schizophrenic's peculiarly disordered thought processes have long been considered the hallmark of his illness. In the belief that currently available tests of abstract reasoning are so contaminated by irrelevant material as to be gross and often misleading measures of thought disorder, an East Coast investigator (5) developed a new (hopefully more precise) test of schizophrenic reasoning processes. The investigator and his group feel that the analogy test they are now in the process of perfecting is not only purer than any of its predecessors but can accurately identify the mechanisms by which people generate analogical relationships. In an ongoing study of 400 hospitalized patients, they are attempting to isolate the various ways in which aspects of the analogical reasoning process go awry, meeting a common end in the schizophrenic aberration of thought.*

*Another East Coast investigator (6) has data to suggest that thought disorder is not the most prominent characteristic of <u>all</u> schizophrenic patients. Some schizophrenics, he believes, show larger deficits in other "ego functions." (A psychoanalytic conception, the "ego" is that portion of the psychological apparatus which integrates one's sense of the real world and one's relationships with people.) Having rated over 100 subjects on 12 ego functions, this investigator has found that schizophrenic patients score significantly more poorly than do normals or neurotics. Since the individual schizophrenic patient may show deficits*

*on any one of a number of ego functions, he contends that disordered thought processes should not be set apart as the preeminent characteristic of schizophrenia. Any attempt to subgroup schizophrenics on the basis of type of thought disorder alone, he warns, fails to consider the dynamic nature and heterogeneity of the schizophrenic syndrome.*

*Many studies have shown that schizophrenics experience difficulty in selectively controlling the input of relevant and irrelevant information from the external environment. It has been hypothesized that, because of a central deficit in the regulatory functions of attention, schizophrenics, unable to protect themselves from sensory input, are "flooded" by auditory and visual stimulation. An NIMH grantee (7), who has been studying information processing and arousal mechanisms in schizophrenics, has data suggesting that these postulated attentional impairments may not be specific to schizophrenia but, rather, an aspect of psychopathology in general. When he compared the performance of two drug-free, hospitalized groups composed, respectively, of schizophrenic and nonschizophrenic psychiatric patients, he found that, while schizophrenics showed greater impairment on an information processing task, schizophrenic and nonschizophrenic patients evidenced comparable disturbance on measures of selective attention and physiological arousal. The nonspecificity (for schizophrenia) of these processes lends further credence to the continuum or "spectrum" notion of schizophrenia with its emphasis on gradations of disorder from neurosis to psychosis.*

*An Intramural investigator (8), who is studying the differences between acute and chronic schizophrenic patients on various measures of social, psychological and physiological functioning, find that acute schizophrenics are significantly more receptive to perceptual stimuli than their chronic counterparts. Among chronic schizophrenics those with little internal intellectual or emotional life do seem to attend to the perceptual environment but become so distracted that they are unable to organize their perceptions in an articulated manner.*

*In testing visual responsivity in a "vision laboratory" (a setting designed to be free of sociocultural and motivational factors), another investigator (9) has shown that hospitalized schizophrenic patients are more sensitive than normals or depressives to very small variations or gradations in photic energy. He speculates that this phenomenon, produced in a relatively "culture-free" environment, may reflect a basic nervous system defect. The schizophrenic's capacity to "do better" than normals (i.e., his greater sensitivity to input differences) may, he believes, have negative survival value; this contention is in accord with the view that the hypersensitive schizophrenic is constitutionally unable to find constancy in the ever-changing stream of his sensory environment.*

*Preliminary data on heart rate and skin temperature collected by in Intramural investigator (10) who is examining psychophysiological patterns in schizophrenics confirm previous electrodermal findings indicating that schizophrenics have higher resting arousal levels than controls but are less responsive to stimuli. Furthermore, arousal tends to be negatively correlated with the patients' performance and positively correlated with that of the controls. Responsivity to demanding stimuli, however, tends to be positively correlated with performance in both groups. In a study of problem-solving efficiency, this investigator found that schizophrenic and control subjects used the various possible decision-making methods with approximately equal frequency and solved problems with nearly the same efficiency.*

*In addition to his reportedly impaired ability to perceive and comprehend environmental "input," the schizophrenic patient's "output" (i.e., his attempts at effective communication) is often considered inadequate. One NIMH investigator (11), for example, has findings which suggest deficits in the speech patterns: In a recent study, he required schizophrenic and normal subjects, matched for I.Q., education and cultural background, to generate verbal monologues. When transcripts of these monologues were presented to normal judges with every fifth word deleted, the judges experienced their greatest difficulty in filling in the missing words from the schizophrenics' speech samples. Furthermore, when these monologues were carefully analyzed for the presence of isolated bizarre intrusions, it was clear that--although such intrusions may have accounted for some of the deficit present--the overall incomprehensibility of the schizophrenic speech samples was structural in nature.*

*Using speech samples emitted by 10 schizophrenic subjects, individually matched with 10 normal controls, another investigator (12) observed that, in schizophrenic speech, strings of interrelated words tend to be relatively short, whereas, in normal speech, sequences of interdependent words extend over much longer spans. As interpreted by the investigator, these results suggest that schizophrenics have a greater tendency than normals to be controlled by immediate stimuli.*

*Other investigators have been examing the nonverbal aspects of schizophrenic communication. For example, one NIMH grantee (13), having developed various indices of kinetic behavior, applied his criteria to videotapes of four paranoid schizophrenic patients and five nonschizophrenic depressed patients. In previous observations of normal subjects, he had identified two main constituents of continuous body-focused movements: 1) hand-to-hand stimulation, frequently associated with the stress of giving verbal associations during an interview, and 2) body touching (exclusive of hand-to-hand contact), apparently linked to the stresses inherent in the interview situation and often a specific response, to a cold, detached listener. In subseqent observations of the two patient groups, the paranoid schizophrenics and the depressives were*

found to perform similarly in terms of total continuous body-focused movements. But when the two primary constituents of body-focused movements were considered separately, schizophrenics showed a prevalence of hand-to-hand and hand-to-fingers stimulation, while depressed patients' movements were primarily classified as body touching. In tracing changes from an acute to a postacute session, the investigator noted shifts in paranoid patients from motor primacy movement toward speech primacy movement--a change characteristically associated with a resolution of the paranoid state. A second movement change in these patients involved an upsurge of body touching, usually in conjunction with the emergence of depressive symptoms. Despite these changes, hand-to-hand movement continued to predominate; its perpetuation seemed to be related clinically to persistence of schizophrenic symptoms. Among depressed patients, the principal change noted was simply a reduction of body touching, a shift concomitant with remission of the depressive state. These pilot observations suggest that motor primacy movement and body touching are kinetic tools which may prove useful in revealing changes in clinical states; hand-to-hand movement, however, is more likely to remain constant within a given patient.

GENETICS

The past decade has seen remarkable progress in the elucidation of genetic factors implicated in schizophrenia's development. Over this period, five exhaustive and methodologically sophisticated twin studies have published findings which are strikingly different from those reported previously. Two famous twin studies published prior to 1960 cited concordance rates (i.e., how frequently both members of a twin pair were diagnosed schizophrenic) of 76 and 86 percent, respectively, in identical twins and of 12 and 17 percent, respectively, in fraternal twins. The five major studies undertaken since 1960, however, found concordance rates varying from 6 to 43 percent in monozygotic twins and from 5 to 12 percent in dizygotic twins. Thus, the genetic contribution to schizophrenia, which based on the early twin studies was felt to be of overriding importance, has gradually been whittled down in size. It is ironic that, as concordance rates have fallen, confidence in the existence of a predisposing genetic factor in schizophrenia has paradoxically increased.

Because twins are almost always raised in the same home, and therefore, share similar environments, the classical twin study method cannot (as many investigators have noted) truly separate the effects of environment and heredity. Another frequent criticism of the use of these studies to indicate a genetic predisposition to schizophrenia's development is that identical twins are apt to be treated more similarly than are fraternal twins; thus, some researchers suspect that the greater rates of concordance found in monozygotic twins may be attributed to psychological, rather than genetic, factors. Unfortunately, this troubling question

*cannot be resolved using the twin study method for the simple reason that twins reared apart (the ideal group for the investigation of genetic factors) occur very infrequently. And, obviously, the additional requirement that at least one member of the separately reared twin pair be diagnosed schizophrenic makes such a sample virtually impossible to obtain.*

*Consequently, investigators interested in the genetics of schizophrenia have lately turned their attention to the adopted-away offspring of schizophrenic parents. In an important series of studies conducted in Denmark, a group of intramural investigators (14) have compared a group of these "high risk" children with a control group composed of 67 adoptees whose biological parents were psychiatrically "normal"; both groups were matched for age, sex, socioeconomic status of adopting family, and age at adoption. Recently, these investigators reported that 14 percent of the offspring of schizophrenic mothers have thus far experienced psychiatric hospitalization as compared with 10 percent of the controls. Moreover, nearly 32 percent of the experimental group, as compared with 18 percent of the controls, received what was termed a "schizophrenic spectrum" diagnosis; this difference was significant at the .05 level. Psychopathological conditions included within this broad diagnostic spectrum ranged from severe neurosis through process schizophrenia. Only 4 percent of the experimental group, however, were diagnosed by these investigators as clearly schizophrenic, and using hospital figures, only 1.3 percent were so diagnosed. None of the controls were considered clearly schizophrenic. Thus, it appears that the biological offspring of a schizophrenic parent raised in an adoptive family is somewhat more vulnerable to the occurrence of psychopathology in later life than is his matched control adoptee. (It should be noted, however, that the incidence of psychopathology in the controls was surprisingly substantial.) Because they found a lower than anticipated rate of schizophrenia (4 percent as compared with an expected 12-15 percent) in the offspring of schizophrenic parents, these investigators infer that adoption may be "protective" to such children--though they add the proviso that, as the mean age for both groups (32) is still within the age of risk (18-44) for schizophrenia's development, more cases of overt schizophrenia in these subjects will in all likelihood occur with the passage of time.*

*In another study, conducted in collaboration with a Jerusalem-based group, intramural investigators (15) studied 50 children of schizophrenic parents and 50 matched controls by means of a very careful and extensive neurological examination (including various tests of perception, coordination, and motor difficulties); the examiners were blind to the respective diagnostic statuses (i.e., normal or schizophrenic) of the children's parents. When each group was divided at the median to form subgroups composed of high and low scorers, comparison of the two high-scoring subgroups revealed that the index cases had significantly higher scores than the controls; no significant differences were found, however,*

*between the two low-scoring subgroups. When the subjects were divided into those above and below age 11, the younger index cases had higher neuropathology scores than the older group. Moreover, no significant differences were found between indexes and controls in the older group. These findings seem to suggest that certain abnormal neuropathological traits detectable at younger ages may disappear (or be muted) as puberty approaches. Concluding that these postulated outward signs of an inherited predisposition to schizophrenia tend to disappear at puberty, the investigators advise that such predispositions be sought in the first decade of life. Whether those children evidencing the greatest number of neurological abnormalities actually develop schizophrenia will not, of course, be known for some years. Thus, this study is an excellent illustration of the difficulties encountered in elucidating explanations (genetic or otherwise) of schizophrenia's origins because of a 20 or more year gap between genetic endowment, which can be inferred but not directly measured, and the symptomatic schizophrenic breakdown.*

*Recognizing the importance of filling in the important intermediate steps between genetic endowment and symptomatic breakdown, another intramural investigator (16) has formulated a "response-disposition" hypothesis. By studying the performance of nuclear family groups and fraternal and identical twins on a series of standardized perceptual tasks, he hopes to learn about the genetics of perceptual style--i.e., the way in which an individual receives, regulates, and modifies environmental and internal stimuli. Since schizophrenia has long been associated with attentional deficits, this investigator feels that perceptual style is an important dimension to consider in the study of schizophrenia. Furthermore, he believes that this effort may aid in the evaluation of the widely accepted but still vague polygenic theory of the genetic contribution to schizophrenia.*

*A group of intramural investigators (17) studying identical twins discordant for schizophrenia found significantly greater than normal catecholamine levels (particularly urinary excretion levels of epinephrine, norepinephrine and dopamine) in both schizophrenic index twins and their nonschizophrenic co-twin controls. Thus, catecholamine levels seem to show a substantial degree of genetic determination and may parallel what can loosely be described as the "genotype" for schizophrenia. In contrast, levels of 17-hydroxysteroids, measured at the same time and under similar inpatient conditions, parallel the "phenotype"; they are significantly elevated only in the schizophrenic index twins, with the nonschizophrenic co-twin controls showing values similar to those found in nonpathological pairs.*

*In conclusion, it can be seen that the genetics of schizophrenia is being approached from a variety of points of view. If additional research in this area continues to receive strong support, one may predict, with some confidence, that a number of unsolved genetic puzzles will be worked out within the next several years.*

*BIOLOGY*

*Basic science has made possible many recent developments in the biology of schizophrenia. In turn, many techniques developed for the study of basic processes in schizophrenia have been applied to a variety of other conditions. Yet, despite this process of mutual stimulation between basic and applied research the biological investigation of this disorder has had a troubled history: Almost annually, "the cause" of schizophrenia has been discovered by some biochemical (or other) procedure. Invariably greeted with great enthusiasm, initial discoveries are all too often followed by failures to replicate and validate preliminary evidence. Thus, cycles of great expectations, questioning, disenchantment, despair and nihilism have been constantly recurring phenomena in the biological investigation of schizophrenia. Two aspects of this process are especially troubling: Initially, the eminently human need for a simple, authoritative answer to a most difficult and frightening problem has frequently led us to embrace too readily, too impetuously, each successive biochemical solution to the schizophrenic conundrum. But, then, when each proffered solution is in turn discredited, a tendency exists for its former adherents, embittered at the loss of the hoped-for total "answer," to dismiss too hastily the very real contributions made to basic science by studies of the biology of schizophrenia (e.g., the use of catecholamine methodology for the study of depression).*

*To many, basic science is an "ivory tower" pursuit--of no real value in developing knowledge directly applicable to schizophrenia. Although investigators have long proclaimed the value of basic science to the field, unfortunately we only rarely can identify, over the relatively short term, directly applicable basic science discoveries. Recently, however, there has been such an advance--developed out of purely basic research. Some years ago an Intramural scientist (now a Nobel laureate) developed a method for the identification of a nonspecific enzyme in the lung of laboratory animals. Using this method as a basis for further work, a West Coast investigator (18) found in chick and human brains an enzyme which was capable of producing a hallucinogen (bufotenin) from serotonin compounds thought to be related, in at least some instances, to the development of schizophrenia. These findings are consistent with the transmethylation theory of psychosis, which suggests that naturally occurring methylated indoleamines (such as bufotenin) as well as others, might be responsible for the severe psychopathology sometimes induced by the administration of large amounts of methyl donor compounds (e.g., methionine). This investigator speculates that, rather than being an hallucinogen producer, this enzyme methylates as a way of deactivating the polar group in the indoleamine compounds which are centrally very active. That is, it may be that the indoleamine N-methyltransferase (the newly found enzyme) is a normal detoxification enzyme which may under special circumstances go astray.*

*Other recent evidence has led a New York investigator (19) to espouse a similar theory, i.e., that abnormalities in the metabolism of some biogenic amines may be associated with the behavioral disturbances seen in psychotic patients. His evidence (more solid now than when the theory was elaborated in the 1950's) consists of the following: 1) Several methylated phenols or catechols, such as mescaline, are capable of inducing psychotic disturbances in man and/or experimental animals. 2) The administration of methionine (a precursor of S-adenosylmethionine, the methyl donor for the O and N methylation of catecholamines) causes psychotic worsening in schizophrenic patients. 3) All effective antipsychotic drugs have markedly disruptive effects on the extrapyramidal system (EPS), which suggests that their therapeutic action may be mediated by this system. Production of EPS disturbances by antipsychotic agents may involve some type of interference with the action of dopamine, believed to be an important mediator of neuronal action in this area of the brain. 4) Restoration of dopaminergic function can be produced by administration of DOPA, a substance which is known to produce psychotic symptoms in some subjects. This suggests that, if the action of antipsychotic agents involves the EPS, then the pathogenesis of psychotic illness may also involve this system. As a working hypothesis (but not an exclusive one), it is proposed that a disturbance in dopamine metabolism could result in the production of an aberrantly methylated compound having mescaline-like effects. In one study which explored this hypothesis by administration of $C^{14}$-labeled NADMPEA (N-acetyldimethoxyphenylethylamine), it was found that this compound was demethylated in the alpha position to NAMT (N-acetylmethoxytyramine) in both schizophrenics and normals. Based on these findings, it was initially concluded that schizophrenics do not have a demethylating defect. This was an important finding because NADMPEA, an extremely powerful compound, behaves as a hallucinogen when administered to rats, demonstrating about 10 times the potency of DMPEA in this regard, and about five times the potency of mescaline. It was therefore of great interest to determine the schizophrenics demethylated NADMPEA to NAMT, which is probably pharmacologically inert, since a failure of such demethylation could have resulted in the accumulation of two potent and potentially hallucinogenic agents--DMPEA and NADMPEA. The same New York investigator has also tentatively demonstrated by examination of rat brains after the administration of NADMPEA in vivo that demethylation of NADMPEA does occur in the brain in vivo. Although the demethylation hypothesis was not supported in his study, this investigator believes that the use of the "model psychosis" paradigm has resulted in significant progress toward an eventual elucidation of some of the central-nervous-system mechanisms which may operate in schizophrenic psychosis.*

*A Midwest investigator (20) reported an interesting series of studies of several muscle enzymes which indicated that 60-70 percent of acute schizophrenic patients, as well as patients with other types of acute*

*psychoses (e.g., manic-depressive psychosis and psychotic depression) had increased levels of two enzymes, creatinine phosphokinase (CPK) and aldolase, in their blood stream. Moreover, approximately 30 percent of the relatives of acutely psychotic patients also had slightly increased CPK activity. Less acutely disturbed patients, on the other hand, rarely evidenced such increases. A number of nonspecific causes for increased enzyme levels in blood have been studied--drugs, activity and tension for example--but none of these appeared to be responsible for the increased levels. Using appropriate chemical techniques, the source of the enzyme was ultimately traced to skeletal muscle. A pair of collaborating investigators then used two different methods to examine muscle biopsies from psychotic patients and controls; neither knew from whom the specimens were obtained. Approximately 70 percent of the psychotic patients' biopsies were considered abnormal, whereas none of the controls' were. It is thought that these muscle abnormalities could, if stress and other factors are ruled out, represent the first tissue evidence of organic disease in acutely psychotic patients.*

*A Northeastern scientist (21) currently has under investigation the claim that schizophrenia is the manifestation of an autoimmune disorder in which a person has built up antibodies to antigens contained in certain regions of his brain. The theory postulates that gamma globulin extracts of the blood serum proteins from schizophrenic patients contain these antibodies and that passive transfer of the disease can be effected by injections of the extracts into normal persons. Indeed, when gamma globulin fractions from schizophrenic patients were injected into monkeys, the electroencephalographic recordings from certain brain areas were reported to have become grossly abnormal and this was often accompanied by unusual behavior. In an attempt to replicate these findings coded samples of serum have been collected from schizophrenic patients and normal persons; gamma globulin extracts are then prepared and injected into the brains of monkeys with electroencephalographic recording electrodes placed in different brain areas. Only after the EEG records have been analyzed is the code revealed. So far, samples from 17 schizophrenic patients and five control subjects have been studied in this system. Eight of 17 schziophrenic patients and two of five normal controls had one or more samplies which yielded positive results as judged by changes in the brain-wave recordings. Thus, the observation has been documented, but its specific relevance to schizophrenia remains unsubstantiated.*

*Investigating a group of State hospital patients, a Midwest scientist (22) reported that female schizophrenic patients may have a relatively high incidence of mosaicisms involving X-chromosome aneuploidies, as compared to the incidence of such chromosomal abnormalities in the*

general population. No evidence has yet been found, however, to indicate that more than a very small minority of schizophrenic patients are affected with genetic mosaicisms. Nevertheless, the relatively high incidence of detected mosaicisms involving X-chromosome aneuploidies affecting buccal cells and peripheral-blood leukocytes in diagnosed schizophrenic patients is suggestive. A large number of nonspecific factors (e.g., drugs, institutionalization, etc.) must, of course, be evaluated before firm conclusions can be drawn.

A West Coast Nobel laureate investigator (23) found that, following 8 days of high-dose vitamin administration, the excretion curves of mental hospital patients showed that their initially lower excretion of test doses (as compared with a mentally well population) was eliminated by the vitamin therapy. These results are difficult to evaluate in the absence of dietary control in both groups; they are compatible with pre-existing dietary intake differences in the two groups. No study of the megavitamins' therapeutic effect was conducted.

A variety of EEG measures are now used in the study of schizophrenia. Of these, the cortical evoked potential has special interest because of its relative freedom from motivational effects. Experiments by a San Francisco group (24) with schizophrenic and nonschizophrenic subjects comparing auditory averaged evoked responses to tone sequences of one pitch and two different pitches indicate that schizophrenics have more variable indivdiual EEG responses to tones, unrelated to pitch. They found no apparent relationship between the EEG measures and drug intake, age or ward behavior. The results are interpreted as reflecting fluctuating attention and a decreased capacity to disregard redundant events in the schizophrenic subjects.

For the past few years a Philadelphia-based group (25) has been using a neurophysiological test procedure based on brain responses evoked by painless electrical stimulation of the median nerve at the wrist. These responses are extracted by means of a computer technique from the larger brain waves in which they are embedded. By varying the strength of the electrical stimuli and the combinations in which they are applied, the procedure attempts to measure the balance between "excitation" and "inhibition" in the portion of the nervous system affected by the stimulus. They found: 1) The normal subject shows a regular variation in amplitude of test responses when the strength of antecedent stimuli is varied. When a relatively strong stimulus precedes the test stimulus, the test response tends to be smaller. The same test stimulus produces a much larger response when the antecedent stimulus is weak. This normal relationship does not hold for the average schizophrenic patient or for patients with psychotic reactions induced by abuse of drugs. It is as though the brain of the psychotic patient can respond only within a relatively narrow and limited range. 2) These investigators felt that there were striking resemblances between the limited brain responsiveness of psychotics and the effects that they observed in experimental studies

*of cats in whose brains electrodes had been implanted for several months. When certain deeper areas of the brain (septal region, reticular formation) were electrically stimulated, the cats' cortical responses were changed; if the prestimulation results were taken as normal, the results after stimulation resembled the findings in schizophrenic patients. 3) As patients showed a loss of psychotic symptoms after treatment, their evoked potential results tended to normalize as well, after drugs were given their results were even closer to normal. In contrast, the evoked potentials of schizophrenic patients who had had little or no response to phenothiazine treatment (since they retained delusions and/or hallucinations) showed no tendency to normalize even after the patients had received drugs for some time.*

*In an extended longitudinal study of sleep in six drug-free acutely ill schizophrenic patients, a group of NIMH intramural program investigators (26) found that all six patients showed severe disruption of sleep in this phase of illness. As a group, they averaged less than 4 hours of sleep and evidenced only one-fourth as much REM (rapid eye movement) as the controls. Reduction in REM percent, REM activity, delta sleep time, and non-REM sleep was marked, and time elapsed from beginning of sleep to first REM period was significantly prolonged. The patients slept only about one-half the possible sleep time available to them, mainly because of difficulty in falling asleep. During the waning phase of illness, normal sleep patterns were gradually restored, although REM time and activity were still reduced. Sleep patterns during remission were very similar to those of the control population. Expected compensatory REM sleep did not follow the severe deprivation which had characterized the waxing stage. In three of the patients, recordings were obtained during psychosis-free intervals just before exacerbation of psychosis. These revealed only minor sleep disturbances. No progressive alterations in any of the sleep parameters appeared prior to the manifestation of psychotic symptoms. These scientists tentatively conclude that the severe and pervasive sleep disturbances in acutely ill schizophrenic patients are nonspecific concomitants of the inner turmoil attending psychotic decompensation and that marked sleep disturbance does not necessarily precede exacerbation of the schizophrenia. They also suggest that delta sleep may be the most sensitive index of the kind of less intense but abiding distress seen in chronic schizophrenia.*

*A West Coast investigator (27) finds that studies of brain-wave activity during sleep have revealed that about 50 percent of patients with schizophrenia showed a marked reduction in the deepest stage (Stage 4) of sleep. This finding is of special interest in view of observations that chlorpromazine, a major antipsychotic drug, increases the amount of Stage 4 sleep. Taken together, these studies provide potential clues to altered brain function in schizophrenia and to the mechanisms of action of antipsychotic drugs.*

*It may be said today that the biology of schizophrenia is less encumbered by the waves of initial over-enthusiasm (and subsequent disenchantment) noted at the beginning of this section. At the same time substantive progress is being made, especially in the development of new methods and the description of a variety of biological abnormalities associated with this disorder.*

*STUDIES OF POPULATIONS AT "HIGH RISK"*

*Traditional research into schizophrenia has sought etiologic clues through the systematic experimental analysis of schizophrenic patients' behavior. This approach, however, contains the following major methodological problem: It is not possible in any study of already manifest, diagnosed schizophrenics to determine whether research results reflect a cause or a consequence of the subjects' illness. To circumvent this problem, the prospective (or high risk) approach is being increasingly used in psychiatric research. This investigative strategy entails the study of a person considered vulnerable to psychiatric breakdown prior to the manifestation of illness. Investigators engaged in high-risk research hope to identify preexisting characterisitics which clearly differentiate between those who later develop schizophrenia and those who do not--clearly an important step in determining this disorder's etiologies. In addition, the identification of individuals at risk would make possible rational preventive intervention--clearly the most important and economically sound public health technique. Because of this twofold potential (for both determining etiology and allowing prevention), the Center for Studies of Schizophrenia has strongly encouraged research in this difficult area. As a result four major new studies have been approved and funded over the past few years, and several others are now being planned.*

*The initial use of the high risk method was made by an American investigator (28), working in collaboration with a group in Denmark. Because its stable population can be traced over a prolonged period of time, Denmark offered an ideal setting for longitudinal research. The study's basic design involved the long-term comparison (over a 20-25 year period) of the children of schizophrenic mothers--the high risk subjects--and those of normal mothers--the controls. Since this study was initiated in 1962, 20 of the 207 high risk subjects (whose average age is now 23) have experienced some type of mental disorder. Subsequent to breakdown, these 20 subjects were compared with two other groups of 20, one selected from among those high risk subjects (i.e., children of schizophrenic mothers) who had not, thus far, experienced mental disorder and the other selected from among the offspring of normal mothers; both comparison groups were matched on a number of characteristics to the "breakdown" group. Based on an initial evaluation in 1962 and on a reanalysis of data subsequent to outcome in 1969, the following characteristics of the "breakdown" group were reported: The children in this group lost their schizophrenic mother to psychiatric hospitals much earlier than*

*did those in their high risk comparison group. Teachers' reports indicated that they tended to be domineering, aggressive disciplinary problems who often created conflicts and disrupted the class with talking-- behavior which distinguished them from both the high risk and the "normal" comparison groups. On the Continuous Association Task, one of a battery of psychological tests given in the initial evaluation, they had a strong tendency to rattle off a long series of interrelated but contextually irrelevant words; in addition, their associations tended to "drift" away from the stimulus word. On psychophysiological measures they showed very rapid response and recovery to stimulation and showed no sign of habituation. Finally, and of great potential significance in terms of preventive measures, 70 percent of the mothers of the sick group had suffered one or more serious complications of pregnancy or childbirth. In sharp contrast, only 15 percent of the mothers of the high risk comparison group and 33 percent of the mothers of the normal control group showed such complications. Although these preliminary findings do not apply solely to schizophrenia (because the majority of the 20 subjects did not suffer a schizophrenic breakdown), they do identify preexisting characteristics which differentiate mentally ill subjects from others. Moreover, if the occurrence of prenatal and birth complications is causally related to the development of mental illness, as this study would seem to indicate, great care should be taken during the schizophrenic woman's pregnancy and delivery.*

*A Midwest investigator (29) has recently reported some very interesting results from another major ongoing study of the children of a schizophrenic parent (either mother or father). In examining these offspring, this investigator and his colleagues found that the degree of a child's maladjustment increased proportionately with the "involving" nature of the parental psychosis. That is, a schizophrenic parent who actively, aggressively approached the child during acute psychosis seemed to produce greater disturbance in the offspring than one who exhibited a pattern of withdrawal and avoidance. In general, therefore, reactive schizophrenics, especially if their spouses were not helpful to the children, produced the most seriously disturbed children. By contrast, the parent with both a "process" type of psychosis and a helpful spouse seemed to produce much less maladjustment in the children. One intriguing finding is that 5 to 10 percent of these "high risk" children react to their family situation with a kind of "supernormality" and became highly interesting, creative, and colorful individuals. As comparison groups, this study included the offspring of normal and of physically ill parents. Some rather surprising results emerged from teachers' ratings and achievement scores in these three groups: Teachers judged the children of physically ill parents as showing more overall maladjustment than those of the psychotically ill parents; predictably the children from normal families were felt to show the best adjustment. The same pattern was found in terms of school achievement. As data continue to accumulate from these two major ongoing studies and from*

the new studies now getting underway, we shall be able to say a great deal more about cause-effect sequences in schizophrenia, about the effect of psychosis on other family members (an important aspect of such studies with today's increasing emphasis on community treatment) and about strategies for rational preventive intervention.

THE FAMILY

Over the past 15 years, many different investigators, using a variety of approaches, have demonstrated rather convincingly the presence of pathological interaction in the families of schizophrenic patients. At this point, however, major disagreement exists as to the relative significance of these findings. Such questions arise as, do the deviant interactional patterns observed antedate the occurrence of illness in one family member? And, if so, are they causally implicated in schizophrenia's development? Or do these deviant patterns simply stem from the parents' efforts to relate to their already strange offspring? When all of these questions are at last resolved, investigators involved in family studies must still confront the thorny problem of determining how one particular participant in a pathological family process develops the overt symptoms of schizophrenia.

By analyzing the stylistic aspects of communication within families, NIMH Intramural investigators (30) have developed measures of "communication deviance" which, over the past decade, have consistently distinguished between the parents and sibs of schizophrenic patients and those of nonschizophrenic psychiatric patients and normal controls. To explore the relationship between the severity of impaired familial communication and the severity of psychiatric illness in the offspring, these investigators compared the communication patterns of parents of 20 process (i.e., unremitting) schizophrenics, 24 acute reactive schizophrenics, 25 borderline schizophrenics, 25 severely neurotic or delinquent patients, and 21 normal controls. Using their measures of communication deviance, they achieved remarkable, almost absolute differentiation among the groups. Not one of the parental pairs with a clearly schizophrenic offspring scored below, and only two of the parental pairs with normal or neurotic offspring scored above, the common median for all parental pairs. Communication scores of borderline schizophrenics' parents were almost equally distributed above and below the median. Only in the case of process (nonremitting) and reactive (remitting) schizophrenics did these measures fail to distinguish between two diagnostic groups.

Another Intramural investigator (31) used a battery of perceptual and cognitive tasks to compare father/mother/patient triads in 16 "schizopresent" families (i.e., families having at least one schizophrenic member) with those in eight psychiatrically normal families. Looked at as a unit, most families with schizophrenic offspring seemed unable to discern underlying patterns and applied very limited or conservative

*generalizations in attempts to impose "order" on the environment. Experimental results indicated that schizopresent families, as a group, interpret events in an oversimplified, inflexible manner. In another phase of his research, this investigator found that, when schizopresent family members worked individually on cognitive tasks, they were able to perform as well as members of normal families, also working individually; when they worked together as a family, however, their performance tended to deteriorate. In contrast, the clarity and accuracy of the normal control family members' cognitions improved in situations involving collective problem solving.*

*Similarly, an NIMH-supported investigator (32) and her long-time collaborator report that parents in schizopresent families interact relatively normally with their "well" offspring; only in the presence of the schizophrenic child does their behavior overstep the bounds of "normality." Whether this abnormal behavior is a direct response to the patient's illness or reflects the parents' customary manner of interacting with their child even before his illness became manifest is an, as yet, unanswered question. One member of the above-mentioned investigative team is presently attempting to resolve this issue by comparing parents of normal and of schizophrenic children as they interact with a sample of unrelated schizophrenic patients. In other studies, which utilize measures of emotional responsiveness and controlling behavior, this pair of investigators found that the speech of normal families reflected greater interpersonal responsiveness and sensitivity than that of schizopresent families. Moreover, their findings were in accord with the frequent observation that members of schizopresent families, particularly those with very disturbed offspring, do not "listen" to each other and are unresponsive and insensitive to the needs and feelings expressed by others. Also interesting was their discovery that the roles played by mothers or fathers in the schizopresent families varied according to the sex of the schizophrenic offspring; this observation tends to support those investigators who contend that the widely held concept of the "schizophrenogenic mother" is an oversimplification of the issue. These investigators also observed that parental "over control" is exercised toward both the patient and his well sibling--a discovery seemingly at variance with the previously mentioned finding that parents of schizophrenic children behaved abnormally only in the presence of the patient. In comparing behavior in mother/patient and mother/sibling dyads, however, they noted that the mothers did seem to be somewhat more "controlling" toward the patient than toward his sibling.*

*An East Coast investigator (33), who required members of normal and schizopresent families to communicate to one another the essential attributes of common household objects, demonstrated that the communication in families of schizophrenics can be distinguished from that in normal families by the greater frequency with which the objects being described were misidentified. He found no significant differences,*

*however, in the respective parental communications directed to the patient and to his well sibling.*

*Another NIMH grantee (34) used a "Revealed Differences" procedure to examine the effects of conflict behavior and reward and punishment on the performance of certain cognitive tasks. Although he found large performance differences between schizophrenic subjects whose parents displayed high or low degrees of conflict, verbal rewards and punishments did not appear to affect the subjects' behavior. Both these variables have been previously reported to produce deficits in the psychological functioning of schizophrenic patients. On a measure of anxiety taken before and after family interactional sessions, the schizophrenic patients appeared surprisingly unaffected by parental behavior which the investigator considered very "noxious." In the course of collecting these data, this investigator and his associates were struck by the fact that the parents in each family studied treated their patient child as if he were even more incompetent and incapacitated than he, in fact, seemed to be. This exaggerated parental protectiveness might stem, they hypothesized, from the child's having been hospitalized and "labeled" as mentally ill. Attempting to test this phenomenon, they studied the performance of normal subjects on a motor task which required the cooperation of a subject who, they were told, was "mentally ill." Surprisingly, the normal subjects performed <u>better</u> with a "mentally ill" collaborator than they did alone or with the assistance of another normal subject. This unexpected result may reflect the fact that the mentally ill (i.e., defective, inadequate) collaborator posed no competitive threat to the normal subjects. It is interesting to note that the normal subjects tended to blame their mentally ill partners for their own performance inadequacies and expressed a preference for "working alone"--even though objective performance measures were at variance with these reactions.*

*In an attempt to approximate "natural," spontaneous family interactions, another East Coast grantee (35) is living with both schizopresent and normal families for periods of 30 days. He will employ naturalistic observation, standardized interview techniques and quantitative analyses of recordings of family interaction to evaluate these families' behavior. Preliminary findings suggest that the two family types differ in "integrative" experiences--e.g., how much time family members spend talking to each other, laughing together, or just "having a good time."*

*In summary, over the last decade and a half research on family processes in schizophrenia has established a number of defects in communication and interpersonal relationships in families with schizophrenic offspring: Although, as noted above, these flaws have not been definitively implicated in schizophrenia's etiology, they have a kind of <u>a priori</u> clinical validity; e.g., it is not surprising that the kind of peculiar communication long noted in an individual patient is also found in other family members. Perhaps the greatest contribution of this body*

*of research is in extending our descriptive horizons beyond the individual patient and thereby focusing attention on, and greatly increasing our understanding of, the broader social context within which schizophrenia develops. Viewed in this perspective, the failure of family studies to provide an answer to the cause-effect question is much less critical.*

*CHILDHOOD SCHIZOPHRENIA AND AUTISM*

*Focused on as a distinct entity only since 1943, childhood schizophrenia is still in the process of being classified and described by many investigators and, like its adult counterpart, remains a relative mystery. Nonetheless, recent research has added substantially to our knowledge of the many neurophysiological and psychological deficits with which it is associated. Schizophrenic children characteristically show marked difficulty in constructing reality and move about in a highly bizarre maner; their speech, thought, behavior and relationships to other people are seriously impaired. But despite these shared characteristics, children suffering from childhood schizophrenia and autism are by no means identical. Indeed, because of the striking differences found among them, much controversy exists over whether childhood schizophrenia constitutes a single disease entity or a whole host of pathological conditions which, while superficially similar, have completely different etiologies.*

*In an effort to assess the relative contributions of neurological and environmental factors to the development of pathology, an NIMH-supported investigator (36) has found that neurologically normal, disturbed children generally come from abnormal family situations, whereas those with neurological abnormalities have comparatively well adjusted families. Moreover, psychiatrists judge the mothers of schizophrenic children with neurological difficulties to be far less seriously disturbed than the mothers of neurologically normal childhood schizophrenics. More recently, this investigator has shown that the kinds of speech and communication difficulties which characterize these children can often be linked to the futile struggle to achieve clear and unambiguous ways of talking within their deviant families.*

*Another NIMH-supported investigator (37) and her associates, who have been examining schizophrenic, brain-damaged and normal children, learned that psychotic children bore a closer resemblance to nonpsychotic brain-damaged children than to normal in 1) electrical rhythms of the brain, 2) learning patterns, 3) intelligence levels and 4) certain biochemical characteristics. Because parents of these three types of children did not differ significantly in their child-rearing practices or personality test responses (though the normal children's parents were felt to be somewhat warmer, happier people), they very tentatively concluded that the role of neurological factors in childhood schizophrenia's etiology is more important than that played by the environment. This group has*

also been studying the peculiar "cross-modal" learning deficit other investigators have noted in these children--i.e., their inability to translate information from one sensory modality (e.g., spoken language) to another (e.g., written language). Since brain-damaged children show similar difficulties, it has heretofore been difficult to relate this shared learning deficit to the marked social unresponsiveness and withdrawal which distinguish schizophrenic children from their brain-damaged counterparts. As it now appears that psychotic children are less able than brain-damaged children to remember things they see, these investigators speculate that poor visual memory could constitute a major obstacle to learning interpersonal and intellectual skills.

Many investigators are attempting to delineate further the biochemical and neurophysiological abnormalities associated with this disorder. One West Coast investigator (38) has evidence suggesting that the area of the brain which controls the sense of equilibrium is deficient in autistic children. He has also shown, using a new technique for obtaining telemetered EEG's, that the brain wave activity found in autistic children is similar to that found in premature babies--suggesting an immaturity in organization of the brain.

Although, by and large, the treatment of schizophrenic children has been disappointing, many investigators have applied "operant conditioning" therapy with some degree of success. This treatment strategy has proved particularly useful in the suppression of self-destructive behavior and in the acquisition of elementary forms of social behavior and language. A West Coast investigator (39), who has pioneered in the use of this technique, concludes that, although it offers some help to almost all disturbed children, it rarely restores them to "normalcy." A major problem is that, to maintain the therapeutic effects of operant conditioning, the treatment environment must generally be continued as well.

Two of the studies cited above (36,37) would seem to yield contradictory results; that is, one reports two "organic" and "environmental" subgroups, while the other cites only an "organic" group. Closer examination, however, reveals that the contradictions are more apparent than real; the children studied by the first investigator represented a much wider age range than those observed by the second. When only the younger, more severely ill children in both studies are considered, the two studies' findings seem more consistent i.e., in oversimplified form, this younger, "sicker" subgroup is a more "organic" one. This brief analysis of discrepancies in two studies illustrates very well some of the difficulties in making across-investigation comparisons of a disorder as heterogeneous as "childhood schizophrenia." The same degree of difficulty exists, it should be noted, in seeking to make similar comparisons between studies of adult schizophrenia. Fortunately, growing numbers of investigators are beginning to describe the

characteristics of their subjects much more carefully, thus allowing analysis of the data on comparable subjects in related studies. This type of advance (i.e., more precise reporting), which all too often passes unnoticed, is crucial to the eventual solution of the conundrums posed by both childhood and adult schizophrenia.

## TREATMENT

Long considered hopelessly incurable, schizophrenia has in recent years proved remarkably amenable to treatment. The major tranquilizing agents, whose powerful impact on the treatment of schizophrenia is indisputable, must be given major credit for the 30 percent decline in the resident schizophrenic population which has taken place since their introduction 15 years ago. But supplementing the phenothiazines' effectiveness has been a concurrent revitalization of "psychosocial" treatment approaches, which also has contributed to the prognostic turnabout. Psychopharmacological studies have convincingly demonstrated the phenothiazines' utility, particularly in the reduction of acute symptoms, but data of comparable depth are generally lacking for the psychosocial approaches. Investigative interest in drugs is now focused on the following questions: What are the differential response patterns of various types of patients to various drugs? What are reliable predictors of response? What are the nature of frequency of undesirable side effects? What are the effects of combining drugs? What are the relative advantages and disadvantages of newly developed somatic agents in comparison with the phenothiazines? Are the drugs' salutary effects enhanced when administered in conjunction with psychosocial therapies? As is noted above, and will be expanded later, this last question has thus far received relatively little attention.

In a large-scale collaborative study conducted by a group of NIMH investigators (40), haloperidol (Haldol), a recently introduced non-phenothiazine psychoactive agent, was compared with a phenothiazine (perphenazine) in the treatment of acute schizophrenic patients. Both drugs were found to be roughly equivalent--both in the reduction of psychotic behavior and in the production of side effects. More recently, an Early Drug Evaluation Unit (41) examined haloperidol's effectiveness (again as compared with phenothiazine) in the treatment of chronic schizophrenic patients. In this study, greater improvement was noted in patients receiving haloperidol, which suggests that this relatively new agent may surpass existing drugs in the effective treatment of chronic patients. But this matter, of course, needs further study.

Using a rating scale designed to measure rate of occurrence of various side effects, a group of East Coast investigators (42) demonstrated that combining perphenazine (a phenothiazine) with amitriptyline (an antidepressant) diminished the undesirable side effects of each, thereby permitting the administration of larger doses of medication. Since

it has heretofore been assumed that combined drug therapy tends only to complicate the clinician's attempts to control side effects, these findings reopen what has been a closed issue. In another study, this Eastern investigative team has shown that a drug's absorption and metabolism varies widely, depending upon mode of administration and intersubject differences. Eventually it is hoped that predictive indices will be developed which allow for the identification of potentially unresponsive or very sensitive patients.

Other investigators are studying psychotropic drugs as a means of clarifying mechanism underlying psychotic process. For example, one NIMH investigator (43) has been examining biochemical changes in several areas of the brain in animals and has shown that the antipsychotic drugs prevent the occurrence of a chain of reactions normally induced by norepinephrine (a neurochemical mediator). Pharmacologically inactive detoxification products of these drugs, however, did not affect the response chain triggered by norepinephrine. These findings present additional evidence that aberrations in the norepinephrine metabolic pathway may occur in schizophrenics.

By studying a cat with implanted subcortical and cortical electrodes, a Southern grantee (44) has demonstrated that several types of antipsychotic drugs can have the same electrophysiological effect in the same anatomical region of the brain; antidepressant drugs, however, have an opposite effect. It had previously been thought that antipsychotic drugs acted principally as inhibitors of arousal in the midbrain, but this investigator has shown that they have both excitatory effects (e.g., in the mesencephalic reticular formation) and inhibitory effects (e.g., in the hippocampus). These findings suggest that neurophysiological measures may provide an animal model for testing new antipsychotic and antidepressant drugs.

First reported clinically beneficial in 1957, niacin remains the subject of controversy; its advocates maintain that schizophrenic patients can be given high doses of this vitamin (over 3 grams per day) without danger of toxicity. To test these claims, a group of investigators (45), working in a collaborative study in Canada, has been examining the effects of nicotinic acid and nicotinamide on a group of newly admitted schizophrenic patients. Thus far, they have found that patients given nicotinic acid or nicotinamide, plus freely administered phenothiazine, did no better (in terms of length of stay and total phenothiazine dosage required) than those given phenothiazine alone. A New Jersey study (46) of discharged patients maintained on niacin is still in progress. Unfortunately, this study's design, entailing extensive followup, precludes reporting of preliminary data. One-year followup data, however, will soon be available.

*Although the value of major tranquilizers to schizophrenic patients is undeniable, there are those who believe they have received undue emphasis as "the answer" to the treatment of schizophrenia. More attention, many practitioners maintain, must be paid to what drugs can and cannot do and to what other factors may be important in an overall treatment program. This question is particularly relevant in light of schizophrenics' high readmission rates and their generally low levels of community adjustment. In addition, recently obtained figures from Denmark and Finland (47), where heavy emphasis is placed on both somatic and nonsomatic treatment, show that no more than 5 percent of the first admission patients diagnosed as shizophrenic will be hospitalized 5 years later (as compared with 15-25 percent here!). The Scandinavians believe their attention to the psychosocial aspects of an overall treatment program is a major factor in the prevention of chronicity. Given the Scandinavians' apparent success in this area, it is unfortunate that so little sophisticated, systematic research on the effects of various psychosocial treatments has been conducted in the United States.*

*In a long-term, well controlled study, a West Coast investigator (48) compared five different types of treatment in 228 first-admission acute schizophrenic patients having uncertain prognoses (i.e., they were neither clearly on their way to rapid remission nor to long-term hospitalization). The treatments investigated were: 1) individual psychotherapy; 2) an antipsychotic drug (Trifluperazine); 3) a combination of psychotherapy and Trifluperazine; 4) electroconvulsive therapy; and 5) milieu treatment alone. Both immediate discharge and preliminary followup (3-4 years) data indicate that patients who received drugs or drugs plus psychotherapy did better and continued to do better, than those who received other treatments. These investigators conclude that tranquilizing drugs alone are the most effective and efficient treatment for hospitalized schizophrenic patients and that individual psychotherapy and milieu therapy alone are the least effective and most expensive and time consuming of the treatments tested. But because the value of human interaction for schizophrenic patients has previously been amply demonstrated (practicularly with regard to the prevention of chronicity) these findings cannot be interpreted as proof that adequate treatment for schizophrenic patients should rely on simple administration of antipsychotic drugs to the exclusion of interpersonal efforts. Vital questions remain unanswered: What kinds of human interaction and intervention, on an individual level and as reflected in therapeutic milieu, will enhance the functioning of the schizophrenic patient? How can such "psychosocial techniques" be best researched? Clearly much work is needed on how to quantify and measure these complex phenomena.*

*Some data are becoming available for a variety of "psychosocial techniques": A Midwestern investigator (49), for example, has been studying the effect of "pairing" in the treatment of chronic hospitalized schizophrenic patients. In an attempt to promote motivation for*

work, mutual interaction and shared responsibility, patients were divided into two-member "buddy" teams; as part of this program, patients received privileges based upon the weekly behavior rating jointly earned by each buddy pair. The results of the study indicated a marked improvement in the behavioral functioning of patients who participated in this project.

The effectiveness of behavior modification techniques in the treatment of chronic schizophrenic patients is being widely investigated. Using a token economy program, a group at a Western State hospital (50) bas focused on rewarding desirable, low frequency behavior (e.g., personal care or work); patients in this project earned 15 tokens for good behavior at mealtime, five tokens for making their beds, 10 tokens for taking their medication, 10 tokens per hour for any occupational therapy, etc. On receiving these tokens, patients could then exchange them for privileges (e.g., cigarettes, watching television, etc.) or necessities. Patients also used tokens to purchase meals, pay room rent, and fines for refusing to comply with requests. After 27 months, 13 of 52 patients had been discharged, and six were working as hospital employees (Group A); of those who remained in the token program, 12 were functioning adequately (Group B), and 12 were still unable to perform as expected (Group C); and nine had been removed from the ward. Clearly this program has affected functioning in a large percentage of these recalcitrant patients.

A Western investigator (51), also attempting to deal with the problem of chronicity, has found that these patients often respond very well to task-oriented group situations. In an effort to see whether such task-oriented groups might be useful in helping patients reestablish themselves in the community, he set up a small "community lodge" in which patients were given major responsibilities in organizing the household, preparing and purchasing food, caring for each other, keeping books, securing employment, etc. As the program progressed, professional staff gradually relinquished their supervisory roles. A group of 75 chronic patients, who volunteered for this program, was compared with a hospitalized group of 75 matched patients who received the usual discharge planning and community assistance, including outpatient psychotherapy, foster home placement, etc. Results for the first 6 months showed that 65 percent of the lodge group and only 24 percent of the control group were able to remain outside of the hospital. Also, 50 percent of the lodge group, as compared with 3 percent of the controls, was employed full time during this period! Over the succeeding 3-1/2 years of followup these rates have remained stable. In addition, the cost for maintaining lodge members was calculated at $6.37 per day as compared with $14.34 per day for the hospital group.

*In another effort to enhance community adjustment and reduce readmission of chronic schizophrenic patients, a Philadelphia-based scientist (52) developed an innovative aftercare program utilizing specially trained laymen. Hospitalized for an average of 10 years, patients in this program manifested the classic symptoms of "chronicity"--apathy, isolation, dependency, lack of available family, and recidivism. Indigenous members of the community, specially trained to help newly released patients deal with the everyday problems of life outside the hospital were assigned therapeutic roles of two types--"live-in enablers" who took patients into their own homes, and "visiting enablers" who regularly visited patients in their apartments and helped supervise their daily activities. At followup 1 year later, patients treated by either live-in or visiting enablers were compared with outpatients who had been treated directly by professional staff. Based on this comparison, it seemed to make little difference whether therapeutic services had been delivered by professional personnel or paraprofessional enablers. Outcome for patients in the experimental group was also compared with that for control patients who, while hospitalized, had participated in a program designed to prepare them for community living; 74 percent of the patients from the community-based treatment group were gainfully employed at followup as compared with only 48 percent of patients from the hospital-based training program. Also interesting is the finding that visiting enablers were generally more effective than live-in enablers.*

*In another effort to tap the therapeutic talents of nonprofessionals, a foster family program (53) has been undertaken as a "town project" in a small Midwestern community--a venture which takes its inspiration from a Belgium community in which townspeople and mental patients have lived together harmoniously for several centuries. After much community orientation, education, and discussion, a number of townspeople have agreed to accept as houseguests newly released "chronic" patients who, prior to discharge, made many trial "visits" in the homes of participating families. Of the 33 patients who have thus far been involved in this program, seven have been placed in foster homes, two are living independently in apartments, four are residing in a boarding home, one is staying with his family, and 11 have dropped out of the program; the remaining eight patients are still participating in preliminary "practice" phases of the project and have not yet been released from the hospital. This program's encouraging preliminary results, together with those obtained in the "enabler study," suggest that nonprofessionals can perform very valuable therapeutic functions. Their success, in fact, raises provocative questions about "professionalism" in mental health. Who, for example, should play a therapeutic role? How much training and supervision is necessary?*

*Indeed, a West Coast investigator (54) has findings which suggest that some aspects of "professionalism" may be antitherapeutic. In a study of nurse-patient interactions on the ward, he found that those nurses*

who were most highly rated by their supervisors were described as cool and aloof by their patients. Based on ward observation, these nurses were less apt than their colleagues to engage in "question-and-answer" conversations or light social banter and were more likely to make suggestions to patients or issue direct orders. Interestingly, the less "professional" the nurse's conduct, the better her patient seemed to like her. The discrepant opinions uncovered by this investigator probably reflect the differing "value orientations" of patients and nursing supervisors and may indicate a need to consult the "consumer" (i.e., the patient) when assessing a nurse's therapeutic impact. It well may be that the importance of "professionalism" in dealing with patients--like many another of our most sacrosanct treatment concepts--is in need of drastic revision.

Current innovations in the treatment of schizophrenia seem more to reflect a return to techniques developed long ago; close person-to-person contact, warmth and understanding without the paternalism inherent in so many doctor-patient relationships, the development of family-like social groups, community orientation and involvement, etc. Interestingly, these changes have been facilitated by the major tranquilizers. In addition to their beneficial pharmacological action these drugs have also had important attitudinal effects. Since the phenothiazines' introduction, mental health professionals have become more optimistic about the schizophrenic patient's outlook for recovery, and this increased optimism has spurred innovations in treatment. Although it is apparent that drugs alone are not a sufficient treatment for schizophrenia we may eventually learn enough about the interaction between their psychopharmacological and attitudinal effects to enhance the effectiveness of our overall treatment programs. In any event, we should not underestimate the contribution of the tranquilizers' indirect attitudinal effects in our evaluations of drug efficacy.

## PROBLEMS AND THE FUTURE

As an entity, schizophrenia faces problems of two different but related types--namely, attitudinal barriers and issues of scientific fact.

A microcosmic reflection of the attitudinal obstacles seen at almost every level of our society is the schizophrenic's symptomatic lack of interest in the world around him. Sadly, the patient's seeming indifference to his fate is all too often paralleled by his family's willingness to relegate his problems to a distant custodial institution, thereby shielding themselves from day-to-day confrontations with this difficult, perplexing disorder. But the tendency to shrink away from the schizophrenic enigma is by no means confined to the patient's immediate family. Perhaps because of the fear madness engenders in each of us, the public at large has never demanded an all-out attack

*on a problem whose very existence they are, by and large, loath to remember. Public apathy is mirrored in the political arena where schizophrenia has traditionally received scant attention. Presently aggravating an already unfavorable situation is the nation's precarious economy: At a time when all Federal spending on health is limited by economic considerations, it is doubly difficult for schizophrenia to compete with currently more popular problems. It is only fair to add, however, that partial responsibility for this neglect must be directed to the scientific community itself, which has historically permitted schizophrenia to be assigned the status of a stigmatized second-class problem. Given these factors, it seems obvious that, if we are ever to develop the kind of comprehensive program so crucial to schizophrenia's ultimate eradication, we must first combat our society's pervasive apathy toward this complex disorder.*

*In the area of scientific fact, the schizophrenic disorder, as always, abounds in controversy. Some of the most pressing issues are detailed below:*

*1. Is schizophrenia single disease or a heterogeneous syndrome? Prevailing opinion favors "multiple entities within the disorder" as the most likely explanation. Should this assumption prove correct, investigators will be released from the need to apply findings to all schizophrenics. But, even if freed of this obligation, investigators still must define and identify the subgroup to which findings do apply--a task that, thus far, has defied completion.*

*2. That heredity plays a role in the development of schizophrenia (in at least some individuals) is rarely disputed; yet the mode of the genetic transmission is unknown. Whether schizophrenia is transmitted by a single gene or reflects a polygenic mode of inheritance is still a mystery, although at present most investigators favor the latter possibility. Granted, "something" may be inherited, but precisely what that something is remains a matter of speculation. Is it an enzyme defect, a biochemical abnormality, a minor neurological deficit, or any one of a seemingly infinite number of factors? If a predisposition is inherited, what is it? How does it operate? What is the nature and course of the spiraling feedback mechanism set up in the individual, his family, and the social system?*

*3. Despite the recent proliferation of studies of family factors in schizophrenia, investigators have as yet been unable to determine whether the phenomena described are products or causes of the illness. Nor is it clear whether these factors are specific to schizophrenia or are more general phenomena associated with any number of psychopathological conditions. The longitudinal prospective study of children thought to be at high risk for the development of schizophrenia should make it possible to deal more adequately with this question of cause and effect--a point of controversy which plagues almost all areas of schizophrenia research.*

4. Infantile autism and childhood schizophrenia are still largely unresolved riddles (indeed, it is not even certain whether they constitute <u>one</u> riddle or <u>two</u>). Although evidence of central nervous system damage in afflicted children under 5 years of age (the group most commonly designated as autistic) continues to accumulate, infantile autism remains puzzling, and childhood schizophrenia, which is most often manifest in later childhood, is more mysterious still. What, for example, is the family's role in the genesis of childhood schizophrenia and/or autism? To what extent are either birth or family factors etiologically significant? The unanswered questions are myriad.

5. The prevailing trend toward community-based treatment of schizophrenia seems certain to accelerate as more community mental health centers and other community alternatives to hospitalization are developed. That being the case, the disturbingly high readmission rates and low levels of psychosocial functioning which characterize discharged schizophrenics (see the discussion on pp. 1 & 2 of the section entitled "The Problem") emphasize the importance of filling in the gaping holes in our rudimentary knowledge of the ingredients necessary to successful community adjustment. To what extent, for example, do familial, somatic, occupational and recreational factors affect the probability of hospital readmission and levels of functioning in the community? Obviously, if these factors' adverse or salutary effects were better understood, it would be far easier to design strategies for minimizing the likelihood of readmission and enhancing community psychosocial functioning in discharged patients.

6. Dealing with the changing roles and character of existing State hospitals looms large as a problem of the 1970's. Because it appears likely that many of these institutions will be phased out over the next few years, research is needed <u>now</u> on how their closing can be accomplished with minimal adverse effects on patients, employees, and the local community. Attention must be directed, too, to the State hospitals which continue to operate. What functions can they legitimately serve, and what kinds of changes, both in physical plant and institutional philosophy, appear to be essential in reshaping the State hospital's role in the treatment of mental illness?

Although beset by the aforementioned apathy and unresolved scientific questions, the quest to understand schizophrenia, and to bring relief to its sufferers, is by no means devoid of encouraging signs. While ameliorative changes in attitude toward schizophrenia are most easily identified in the scientific enclave, headway has been made among laymen as well--as evidenced by their increasing tolerance of patients in the community. Indeed, it seems safe to predict that the longstanding pessimism surrounding this disorder may gradually give way to a more optimistic view--a development which will bode well for the eventual solution of mental health's most stubborn conundrum.

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